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Transposition des gros vaisseaux
Transposition of the great arteries

Etudiante
Mme Kampmann, Lisa

Tuteur
Dr. Di Bernardo, Stefano
Médecin adjoint, MER
Service de cardiologie pédiatrique – CHUV

Expert
Prof. Müller, Olivier
Chef de service, Professeur ordinaire
Service de cardiologie – CHUV

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Introduction

Transposition of the great arteries (TGA) is a congenital cardiac defect in which the aorta arises entirely or largely from the right ventricle (RV) and the pulmonary trunk arises entirely or largely from the left ventricle (LV). This is known as a ventriculo-arterial discordant connection(1).

There are two different forms of TGA, complete TGA and congenitally corrected TGA (ccTGA). In ccTGA (also named L-TGA), the atrio-ventricular and ventriculo-arterial connections are discordant, the lower part of the heart being 'inversed'. Due to this double discordance, we can observe a 'physiological' correction of circulation with however, a systemic right ventricle(2) *(Figure 1)*. It is different from and much less common than complete TGA (also called dextro-TGA or d-TGA).

Figure 1 – Congenitally corrected TGA

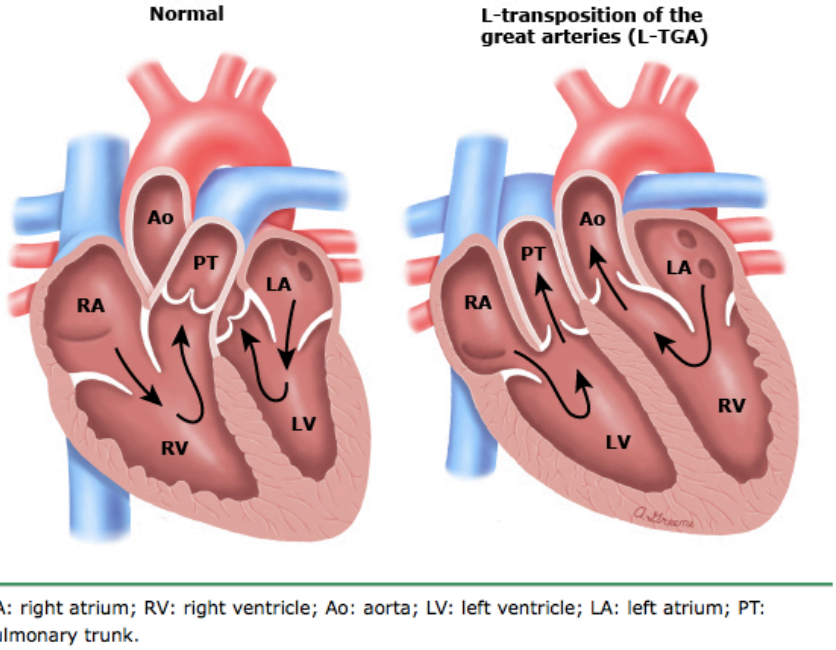

Figure 1 - *I. Normal heart II. L-TGA (cc-TGA). Source: UpToDate, Inc.*

This master is going to focus on complete TGA, or d-TGA which will be referred to simply as TGA. It applies to cases, as mentioned above, with a ventriculo-arterial discordant connection and an atrioventricular concordant connection. As a result, the systemic and arterial circulations run 'in parallel' rather than 'in series'(3). Complete TGA is incompatible with life unless there

somehow is a connection between the two circuits in order to allow oxygenated blood to flow in the aorta(2). This creates a shunt. It can be seen in the form of an atrial septal defect (ASD), a ventricular septal defect (VSD) or a patent ductus arteriosus (PDA)(4)*(Figure 2)*.

Figure 2 – Complete transposition of the great arteries

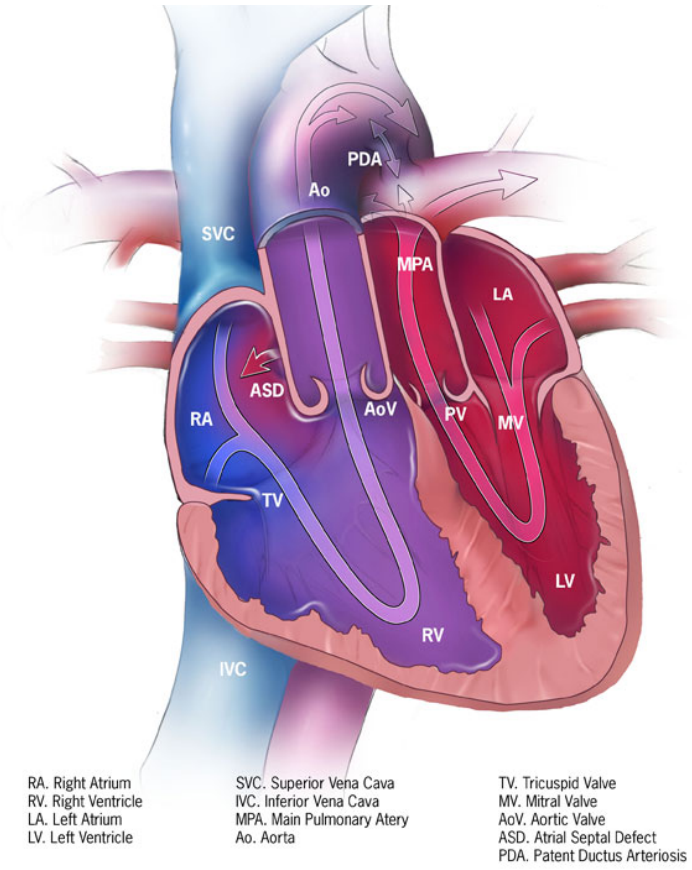

Figure 2 – *D-Transposition of the great arteries. Source: US Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities)*

Due to increased availability of improved ultrasound technology in the past decade, the rate of prenatal diagnosis for all congenital heart diseases has increased, including TGA(5). This master is going to focus specifically on the impact of prenatal diagnosis on different outcomes such as perinatal and perioperative care, long term outcomes and mortality.

TGA represents 5-7% of all congenital cardiac diseases with an incidence of 20-30 cases per 100'000 live births. The male to female ratio is 4:1(6). It is one of the most common cyanotic congenital heart defects(4). TGA is not typically associated to syndromes, however in 65% of cases we can observe coexisting cardiac abnormalities(1).

Historically

TGA and its morphology was first described by Baillie in 1797, calling it 'a singular malformation in which the pulmonary artery arises from the left ventricle and the aorta from the right ventricle'(7). Then in 1814, Farre coined the term 'transposition of the aorta and pulmonary artery' to describe the fact that each artery is 'placed across', 'trans' meaning 'across' leading to the term of transposition(8).

Fanconi and Taussig were the first to recognize TGA during life, in 1932 and 1938 respectively(1).

In 1950 cardiac surgery for TGA began at Johns Hopkins Hospital with Blalock and Hanlon. They described atrial septectomy whose purpose was to mix pulmonary and systemic venous return at an atrial level(9). An atrial septal defect was created through lateral thoracotomy, the atrial septum was grasped, withdrawn, and excised(10). This surgical technique was widely practised.

Later, in 1966 Rashkind and Miller introduced balloon atrial septostomy (BAS) a nonsurgical procedure to create an atrial septal defect, using a balloon catheter. The purpose of this technique is also to mix pulmonary and systemic blood, however the access is via the femoral or umbilical vein(11). This technique was later modified by Park(12).

In 1953 what is now known as the Baffes operation was invented by Lillehei and Varco. The essence of this technique was to anastomose the right pulmonary veins to the right atrium and the inferior vena cava to the left atrium(13).

Many attempts at surgically repairing TGA were made during the second part of the 20th century. A notable technique is the Senning procedure where the atrial wall and septum are restructured as to accomplish transposition of venous return at an atrial level(14).

In 1963 another breakthrough was seen with the Mustard procedure; the idea was to create a larger atrium than with the Senning procedure. This was achieved by excising the atrial septa and using a pericardial baffle to redirect systemic and pulmonary flow(15).

Results of the Mustard or Senning procedures proved to be better on children of 6 months or older. It was important to find an early palliation technique by creation of an intra-atrial communication. This is where the Blalock-Hanlon or Rashkind procedures come in. They allowed a mix of pulmonary and systemic venous flow at an atrial level. The infants operated by Blalock-Hanlon or Rashkind then underwent a Mustard or Senning procedure later on(11).

As the Rashkind procedure had better success rates it eventually replaced the Blalock-Hanlon technique(16).

A revolution in the surgical treatment of TGA happened in 1975 when Jatene and colleagues started using an arterial switch technique now called the Jatene procedure(17).

Today, the arterial switch operation is recommended for most TGA patients (see *Treatments*).

Anatomy

Atria

A larger right atrial size can be seen in TGA, mostly in patients with an intact ventricular septum. Mostly, the atria develop normally(1).

Ventricles

The aorta arises from the right ventricle. In 90% of cases the aorta is positioned to the right and anteriorly to the pulmonary trunk (PT). The PT is leftward and posteriorly positioned to the aorta. They ascend in a parallel manner(1). In rare cases, the aorta is directly posterior to the PT(18).

In anatomically correct hearts, the left ventricle (LV) is thicker than the right ventricle (RV) in utero already. After birth, the LV wall thickens gradually whereas the RV wall becomes relatively thinner(19).
Ventricular wall thickness differs in TGA hearts compared to normal hearts. In TGA, the pressure is augmented in the RV due to its systemic origin and lower in the LV due to its pulmonary origin. This higher pressure in the RV will cause muscular hypertrophy and inversely for the LV. In hearts with an intact septum the LV thickness is normal at birth but its growth stalls resulting in a lower than normal thickness after a few months of life(20). On the other hand, LV wall thickness in TGA hearts with VSD stays within normal range due to pressures in RV and LV equalizing through the VSD(19).

Coronary arteries

In normal hearts, the left coronary artery (LCA) arises from the left posterior aortic sinus and the right coronary artery (RCA) arises from the anterior aortic sinus. This differs in TGA. Usually in TGA, the coronary arteries arise from the aortic sinuses that face the pulmonary trunk. This means the LCA will arise from the left posterior aortic sinus and the RCA from the right posterior sinus(1). They have been renamed sinus one and sinus two respectively(21). The anterior sinus is therefore the non-coronary sinus(22).

Coexisting cardiac malformations

As mentioned above, approximately 65% of TGA patients also suffer from a coexisting cardiac anomaly.
In this subsection, the most common coexisting cardiac malformations will be described.

i. Ventricular septal defect (VSD)

A ventricular septal defect is a hole or multiple holes in the interventricular septum(1)*(Figure 3)*.
50% of patients suffering from TGA will have an associated VSD.
In normal hearts, the left ventricular pressure is higher meaning the larger the ventricular septal defect, the more of this left ventricular pressure will be transferred to the right ventricle. When the defect is more than 50% of the area of the aortic root, the pressure in both ventricles equalizes(23).
In TGA the presence of a VSD will significantly alter clinical presentation as it allows a certain degree of inter-circulatory mixing (see *clinical presentation* chapter).

Figure 3 – Ventricular septal defect

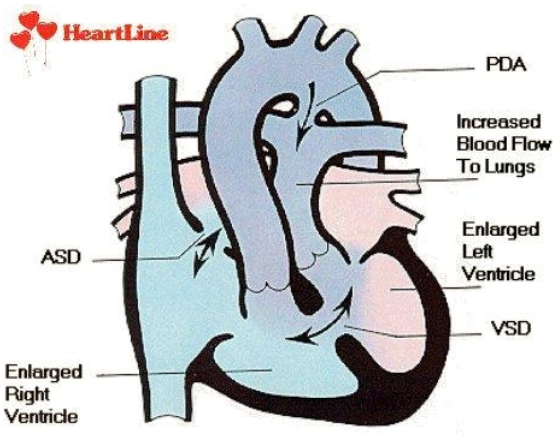

Figure 3 - *Transposition of the great arteries with concomitant ventricular septal defect and a patent ductus arteriosus. Source: Grech et al. – 1999 – Cardiac illustrations.*

ii. Patent ductus arteriosus (PDA)

The ductus arteriosus is a vessel connecting the thoracic aorta with the left pulmonary artery during foetal life in order to bypass the non-functioning lungs, it most commonly closes at birth and becomes the ligamentum arteriosus *(Figure 4)*.

Maintaining ductal patency is vital for infants who have TGA as it provides a source of inter-circulatory mixing. Postnatal closure of the ductus arteriosus may lead to acute decompensation in the neonatal period with profound cyanosis. A continuous infusion prostaglandin E1 is necessary for maintaining duct patency(24).

Soo et al. reported a case where the ductus arteriosus was kept open via ductal stenting in order to maintain sufficient oxygenation and stable hemodynamics(25).

Figure 4 – Foetal circulation in transposition of the great arteries

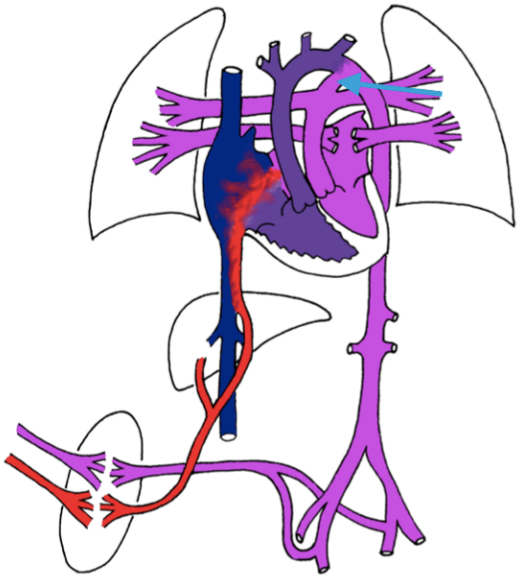

Figure 4 - *Foetal circulation in transposition of the great arteries. Arrow indicates the patent ductus arteriosus. Source: Johnson et al. – 2005- Delivery Room and Early Postnatal Management of Neonates Who Have Prenatally Diagnosed Congenital Heart Disease(24).*

iii. Left ventricular outflow tract obstruction (LVOTO)

LVOTO is defined as an echocardiographic peak of left ventricular outflow gradient above 20mmHg associated with a dynamic or anatomic narrowing(26).

Many patients with TGA will develop LVOTO. A small percentage (0.7%) of patients with TGA and an intact septum have LVOTO at birth or a few days after birth whereas most patients develop it with time leading to an overall prevalence of 30 to 35%(27)(28).

Due to the origin of the PT from the left ventricle in TGA, LVOTO causes a sub-pulmonary obstruction. LVOTO can be of a dynamic or anatomic nature.

- Dynamic type of LVOTO in TGA patients with an intact septum is due most commonly to the leftward bulging of the septum(27). This is explained by the augmented pressure in the RV compared to the LV which creates muscular hypertrophy and a leftward bulge of the interventricular septum(29).
- Anatomic type of LVOTO in TGA patients who also have a VSD is usually sub-valvar and valvar such as a localized fibrous ring or annular hypoplasia respectively.

iv. Valvar anomalies

- Mitral: approximately 20 to 30% of TGA hearts have a mitral malformation(30) although more than 50% of them are not considered to have an effect on cardiac function(31).
- Tricuspid: there exists tricuspid anomalies in TGA patients but they are less common than those of the mitral valve(32).

Clinical Presentation

Neonates with TGA are typically full-term(23), with a normal or above average birth weight(33). They also tend to have increased anteroposterior chest dimensions due to hyperinflation of the lungs(34).

Having two parallel closed circuits results in significant hypoxemia which is observed clinically by central cyanosis. The bluish discoloration of the skin and mucous membranes is therefore the basic pattern of clinical presentation in TGA(35). The onset and severity depend on the degree of mixing between the two circulations.

As mentioned, without a mixing of pulmonary (Qp) and systemic flow (Qs), this malformation is not compatible with life. A shunt is created through the PDA or a VSD in cases where it is present. The net volume of blood exchanged between the two parallel circulations must be isovolumetric or the donor circulation is rapidly depleted and the recipient is rapidly over-loaded(34). Clinical presentation will vary depending on the degree of mixing between the two circulations. Degree of mixing is the magnitude of bidirectional shunting which is highly variable from case to case(1).

i. <u>Poor mixing (Intact ventricular septum)</u>

   These patients have an intact ventricular septum. An atrial septal defect (ASD) or a patent foramen ovale is usually seen(36). Cyanosis will appear within a few hours or a few days for 90% of these infants. It is rapidly progressive(37).

   Tachypnea and tachycardia is rapidly observed. If left untreated the infant will die of hypoxia and acidosis without signs of frank heart failure. This rapid downhill is slowed if a large ASD is present(38).

ii. <u>High mixing (Large VSD, PDA or both)</u>

   Due to the high degree of mixing, the clinical symptoms tend to appear in the second part of the first month of life. These infants present with mild cyanosis and signs of heart failure due to pulmonary venous hypertension. There is a high pulmonary blood flow (Qp) due to the presence of a large communication at ventricular or ductus level, or both. A high Qp provides a large volume of oxygenated blood that will then be passed

to the systemic circulation via the PDA, VSD or both(39). These patients have a systemic arterial saturation (SaO2) of at least 70%(36).

iii. Poor mixing and low pulmonary blood flow (large VSD and LVOTO)

Cases of TGA with a large VSD and LVOTO is rare. The LVOTO causes a low Qp meaning there will be poor mixing. Due to the low Qp there will be no pulmonary hypertension and no signs of heart failure. On the other hand, there will be signs of severe pulmonary stenosis and pulmonary atresia(1). Having a low Qp will lead to a low volume of oxygenated blood. A lower volume of oxygenated blood reaching the systemic circulation causes hypoxemia(34).

Treatments

The survival of TGA patients has drastically improved. If left untreated infants do not survive the first year of life. This rise in survival rates is attributed to initial medical management consisting of a continuous prostaglandin infusion and balloon atrial septostomy (BAS) followed by a corrective surgery. The arterial switch procedure is the corrective surgical procedure recommended in most cases of TGA.

As mentioned, the initial treatment for TGA is a continuous infusion of prostaglandin E1 (PGE1) to maintain the patency of the ductus arteriosus in order to allow some oxygenated blood to reach vital organs(40).

The arterial switch operation has become the preferred option for treating TGA. In certain cases, the arterial switch procedure cannot be implemented early enough. In these cases, in order to maintain a connection between the pulmonary and systemic circulation (no longer sufficient with the continuous prostaglandin E1 infusion), a balloon atrial septostomy (BAS) is necessary(41).

A BAS *(Figure 5)*, also called a Rashkind procedure, can be performed under sedation or general anaesthesia. The access is via the femoral or the umbilical vein. A balloon catheter is advanced into the right atrium. The foramen ovale is then crossed and the catheter is positioned in the left atrium. The balloon is inflated then sharply withdrawn in the right atrium and quickly deflated. This manoeuver can be repeated several times, the efficacy can be immediately seen by the rise in oxygen saturation(11).

Figure 5 – Balloon atrial septostomy

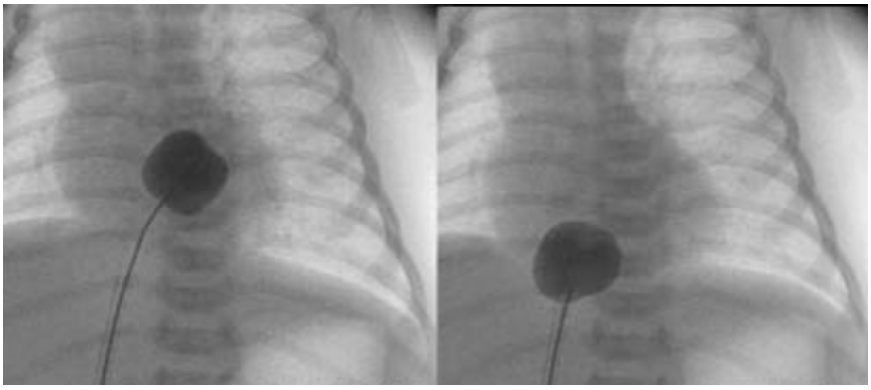

Figure 5 - *Balloon atrial septostomy under fluoroscopic guidance in the frontal projection. Source: Boehm et al – 2006 Balloon atrial septostomy: history and technique(11).*

In patients with TGA as their only cardiac defect, the arterial switch operation (ASO) is the recommended procedure *(Figure 6)*. In most cases, the ASO has replaced the earlier atrial switch procedures developed by Mustard and Senning (see *Historically*).
In patients with TGA and a VSD, the preferred approach is an ASO and VSD closure. In patients with TGA, a large VSD, and significant pulmonary stenosis an alternative surgical approach, should be considered(42).

The ASO is done under cardiopulmonary bypass. The aorta and the main pulmonary artery are transsected above the semilunar valves. The coronary arteries are excised from the aortic root with a button of aortic wall and relocated on the native pulmonary root. The pulmonary arteries are dissected down to the pulmonary hilum to allow the translocation of the pulmonary bifurcation over the ascending aorta (Lecompte manoeuvre). The native pulmonary root (now the neoaortic root) is anastomosed to the ascending aorta. The native aortic root (now the neopulmonary root) is anastomosed to the pulmonary artery. Atrial and ventricular septal defects are then closed. Cardiopulmonary bypass is now discontinued and heart function is regained(43).

Figure 6 – Arterial switch operation

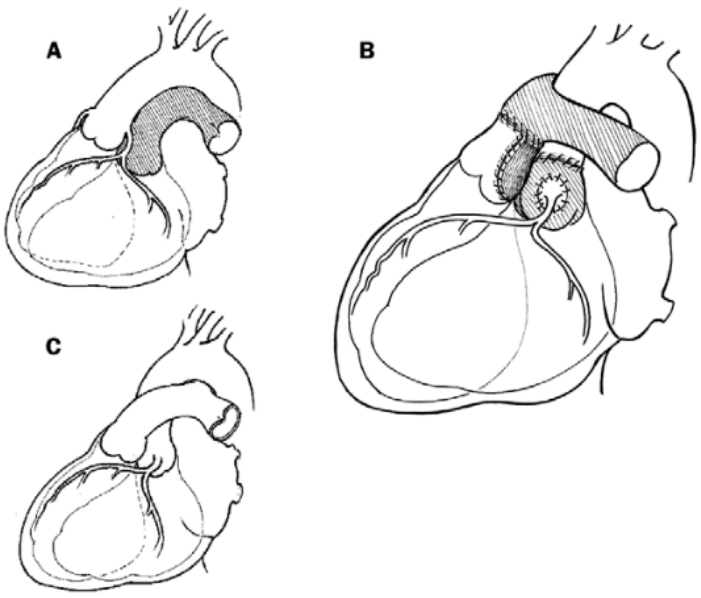

Figure 6 - *Diagrammatic representation of the arterial switch operation.* ***A:*** *Transposition of the great arteries* ***B:*** *Arterial switch operation. Note translocation of coronary arteries on the neoaorta, the position of the pulmonary bifurcation over the ascending aorta, and the repair of the pulmonary artery after harvest of the coronary arteries.* ***C:*** *Normal Heart.*

Source - Prêtre et al. - 2001 - Results of the arterial switch operation in neonates with transposed great arteries(43).

Diagnosis

Postnatally, TGA diagnosis relies on the clinical suspicion of a cyanotic cardiac disease, the main symptoms and signs being cyanosis, tachypnea and a murmur (see *Clinical presentation*) associated with a diagnostic echocardiography.
Due to the increasing rate of prenatal diagnosis for congenital heart diseases such as TGA, this master is going to focus on its effects on various short and long-term outcomes.

Prenatal diagnosis

The rate of prenatal diagnosis of all congenital heart diseases has increased over the past decade with improved ultrasound technology and availability(5)*(Figure 7)*. However, the question of whether prenatal TGA diagnosis affects patient outcome is still source of controversy.

Figure 7 – Trends in prenatal diagnosis

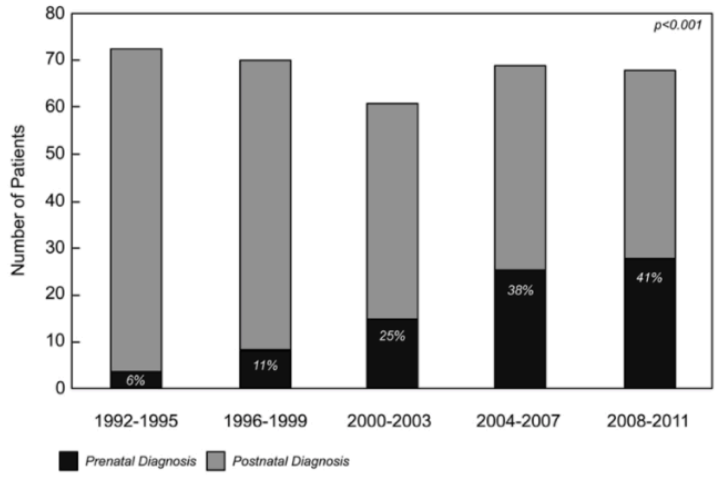

Figure 7 - *Trends in Prenatal diagnosis - Source: Escobar-Diaz et al. - 2015 - Prenatal Diagnosis of Transposition of the Great Arteries over a 20-Year Period: Improved but Imperfect(44).*

A study by *Bonnet et al.* in 1999 concludes that prenatal diagnosis reduces mortality and morbidity, and that prenatal detection rates must be increased to improve early neonatal management of TGA(45). Similarly, a UK based study by *Blyth and al.* shows data that suggests improving antenatal diagnosis could lead to a significant reduction in the mortality associated with TGA(40).

On the other hand, some studies find no evidence that prenatal diagnosis improves survival, such as the 2016 study by *Debost-Legrand et al(46)*. *Lara et al* describe no association between prenatal diagnosis and neonatal mortality in infants with isolated TGA(47).

This section will discuss the modalities of prenatal diagnosis and the different studies which have investigated its impact on different outcomes such as perinatal and perioperative care, long-term outcomes and mortality.

Foetal echocardiography in TGA

Prenatal diagnosis (PND) in TGA consists of prenatal echocardiography *(Figure 8,9 & 10)*. It is being performed with increasing frequency to detect all congenital heart diseases(48). The frequency of detection is rising due to an increasing number of routine antenatal scans, a French study has shown a detection rate as high as 72% between 1995 and 2000(49). There has been recent adaptation in screening protocols which associated with advances in obstetrical echographic technology account for the increase in prenatal detection. This is not the case worldwide, the rate still being between 20% and 60% depending on the studies(50,51).

The main cardiac structures can be observed by ultrasound at 12 weeks' gestation, however in order to have a more detailed view of the foetal heart, a routine morphologic ultrasound is performed between 18 and 24 weeks' gestation(52).

Basic screening echocardiography includes multiples views which are:

- The four-chamber view
- The left ventricular outflow tract view (also called five chamber view)
- The right ventricular outflow tract view
- The three-vessel and trachea view
- Aortic and ductal arch view

In a detailed foetal echocardiogram, are included:

- The M-mode (mostly for arrhythmias)
- Doppler imaging
- Colour-flow imaging

Figure 8 – Foetal echocardiography, TGA (I)

Figure 8 - *Freire et al. 2012 - Colour Doppler evaluation in a foetus with TGA depicting a parallel course of the great vessels with the Aorta (Ao) arising from the anterior right ventricle and the pulmonary artery (PA) arising from the posterior left-sided ventricle. The patent arterial duct (PDA) is also seen(53).*

A complete diagnosis of TGA is now possible by 18 weeks' gestation with 95% confidence with foetal echocardiography(53).

The vast majority of TGA cases show a normal image on a four-chamber view except cases with co-existing malformation such as a VSD(53,54) . This explains why TGA cases with co-existing anomalies have a higher rate of prenatal detection(53).

It is essential to visualize the great arteries and outflow tracts, the diagnosis being dependent on the operator's ability to analyse them. On an extended outflow tract view, the presence of parallel great arteries (also seen on colour-flow imaging), a failure of the great vessels to cross each other and an aorta anterior and to the right of the pulmonary artery are reliable clues in the diagnosis of TGA. The presence of two vessels (transverse aortic arch and superior vena cava) in the three vessel view and a posterior branching of the pulmonary artery from the LV with a superiorly branching aorta from the RV are also important signs in the diagnosis of TGA(53,54).

Figure 9 – Foetal echocardiography, TGA (II)

Figure 9 - Freire et al. 2012 - Parallel origin of the great vessels in grey scale. The patent arterial duct is shown to connect the aorta (Ao) to the pulmonary artery (PA)(53).

Figure 10 – Foetal echocardiography, TGA (III)

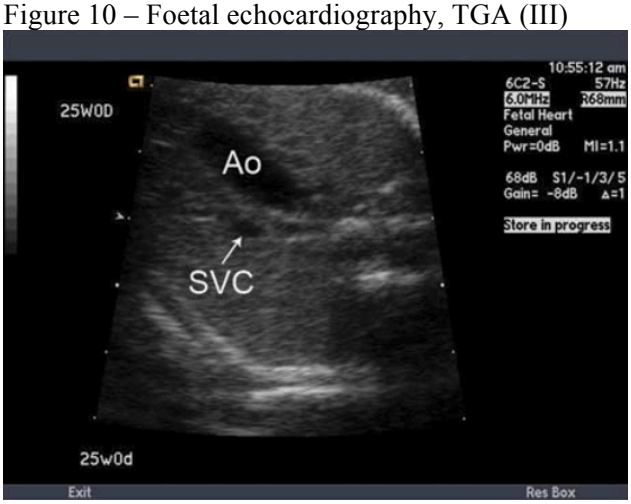

Figure 10 - Freire et al. 2012 - The three-vessel-trachea view in greyscale in a foetus with TGA demonstrating the aorta (Ao) as a single large vessel with the superior cava vein (SVC) to the right(53).

Factors influencing diagnostic

A French study analysing the factors influencing diagnostic found that maternal obesity was significantly more frequent in the postnatal diagnosis group and concluded that maternal obesity is one of the main causes of missed prenatal TGA diagnosis(55).

Debost-Legrand et al also compared prenatally and postnatally diagnosed cases of TGA and found that the main characteristics of mothers and pregnancy did not differ. However, overweight women were more numerous in the post-natal group although it did not reach statistical significance(46).

Short-term morbidities

1. Influence on perinatal care

Raboisson et al. conducted a study in which they compared different variables between a group of TGA patients diagnosed prenatally (PND+) or postnatally (PND-). They looked at the **rate of spontaneous labour**. Their conclusions were; PND+ patients had a lower rate of spontaneous labour and a higher rate of **caesarean sections** (nearly three times higher in the PND+ group). **Induction of labour** was 2.5 times as frequent and labour was induced 1.5 weeks earlier associated with lower birth weight and height for those diagnosed prenatally. They also compared the time it took for the neonate to arrive in an intensive care unit (**ICU**), it took a mean of 2h30 for the PND+ group and 26h for the PND- group *(Table 1).* There was no difference as to saturation, blood pressure or prostaglandin infusion at admission. A higher percentage of patients had to have mechanical ventilation in the postnatal group but the difference was not significant(51).

Bartlett et al. also observed a lower incidence of spontaneous labour in PND+ patients, higher rates of **induced delivery** and no foetal distress during labour which wasn't the case in the PND- group. In this study, **Apgar scores** were compared with no significant differences at one minute scores however, the PND+ group had significantly lower Apgar scores at five minutes. It is important to note that infants in the PND+ group had a lower gestational age and a significantly lower **birth weight**(48)*(Table 1)*.

Escobar-Diaz et al on the other hand found no statistically significant differences in gestational age at birth or birth weight between the two groups(44).

Table 1 – Influence of prenatal diagnosis on perinatal care

Study	Year	PND (%)[1]	Outcome	PND +	PND-	P value
Raboisson et al.	2009	40.0	Induced delivery (%)	54.1	19.4	<0.0002
			Delivery (WG[1])	38.7	40.2	<0.002
			C-Section (%)	31.2	8.2	<0.001
			Mean time to ICU[3] (mins)	2h30	26h	<0.001
Bartlett et al.	2004	7.2	Induced delivery (%)	44	20	=0.004
			Mean birth weight (g)	3320	3501	=0.008
			Apgar score at 5 mins	8.0	8.3	=0.01

[1]PND (%) represents the percentage of TGA patients who were diagnosed prenatally out of all TGA cases in each particular study
[2]WG: Weeks of gestation
[3]ICU: Intensive care unit

2. Influence on perioperative care

The balloon atrial septostomy (BAS) also called Rashkind procedure consists of enlarging the foramen ovale with a balloon to allow mixing of the systemic and pulmonary circulation to better saturation. This can be done via the umbilical or femoral vein. The **umbilical approach** is associated with lower morbidity and is considered an easier and shorter procedure. The PND+ group had a higher rate of umbilical versus femoral approach in the *Raboisson et al.* study. The **success rate** of each procedure was higher in the PND+ group, independently of the approach(51)*(Table 2)*.

In the *Escobar-Diaz et al.* study, it is shown that PND+ patients underwent a **BAS** at 0 days postnatal whereas the PND- were operated one day later *(Table 2)*. There was no statistically significant difference between the need for extracorporeal membrane oxygenation (ECMO) pre or post operatively, nor the length of ICU stay(44).

PND+ patients were significantly more likely to have undergone **endotracheal intubation (EI)** in the preoperative period according to *Bartlett et al* (48). This was not the case in the *Escobar-Diaz et al* study(44). The two groups of *Bartlett et al* were similar with respect to intraoperative variables such as circulatory arrest, total bypass time and total support time. The same can be said for postoperative variable such as days with EI, days in the ICU and total

days in hospital. This being said, PND+ patients underwent surgical repair 5 days earlier than PND- neonates. Surgical repair in this case consists of the **arterial switch operation**(48) *(Table 2)*.

In the 2012 study by *Calderon et al* both short-term and long-term outcomes were analysed using a screening process of all children born with TGA between 2003 and 2005 at the Necker Children's Hospital in Paris. They had 64% of PND+ patients for 36% PND-. Both groups were compared and did not differ significantly in the incidence of preoperative, intraoperative and postoperative variables. This being said, patients in the PND+ group had a significantly lower rate of **acidosis** (3% vs 18% in the PND- group)(56).
Escobar et al found a higher rate of acidotic patients in PND- patients, however the difference was not statistically significant(44)*(Table 2)*.

A study by *Peyvandi et al*, compared the prevalence of preoperative **brain injury** in neonates suffering from congenital heart diseases with or without PND. They had 153 cases, 96 with TGA and 57 with single ventricle physiology. Out of the 96 TGA cases 68 were PND+. They measured the rate of brain injury, more specifically, white matter injury, stroke and hypoxic-ischemic injury. All were lower in the PND+ group. All put together, PND+ patients had 21% of preoperative brain injuries whereas PND- had 46%(57)*(Table 2)*.

In 2015 *Van Velzen et al.* evaluated the effect of PND on perioperative outcomes. They observed a significantly higher **oxygen saturation (SpO_2)** in PND+ patients as well as a lower **rate of renal dysfunction.** There was no closure of the formerly **patent ductus arteriosus (PDA)** before prostaglandin (PGE) infusion in the PND+ group which was not the case in the PND- group(58)*(Table 2)*.

Table 2 – Influence of prenatal diagnosis on perioperative care

Study	Year	PND (%)[1]	Outcome	PND+	PND-	P value
Raboisson et al.	2009	39.7	UA[2] vs FA[3] rate (%)	81	66	<0.05
			UA success rate (%)	81	51	<0.001
Escobar et al.	2015	23.8	Age at BAS[4] (days)	0	1	<0.001
			Metabolic acidosis rate (%)	16	26	Ns[*]
			EI[5] rate (%)	56	69	<0.005
Bartlett et al.	2004	7.2	EI rate (%)	96	77	=0.02
			Metabolic acidosis rate (%)	16	20	Ns
			Age at arterial switch (days)	4	9	<0.001
Peyvandi et al.	2016	70.8	Any brain injury[6] rate (%)	21	46	=0.03
Calderon et al.	2012	64.4	Metabolic acidosis rate (%)	3	18	=0.04
Van Velzen et al.	2015	24.5	SpO_2[7] (mmHg)	73.5 ± 15.9	67.0 ± 15.5	=0.048
			Renal dysfunction rate (%)	4.3	19.1	=0.039
			DA[8] closure before PGI[9](%)	0	23.6	<0.0001

Values are mean or percentage
[1]PND (%) represents the percentage of TGA patients who were diagnosed prenatally out of all TGA cases in each particular study
[2] Umbilical approach. [3]Femoral approach of Rashkind procedure (balloon atrial septostomy)
[4]Days after birth to balloon atrial septostomy
[5] Endotracheal intubations
[6] All preoperative brain injuries
[7] Oxygen saturation
[8] Ductus arteriosus
[9] Prostaglandin E1 infusion
[*]Not significant (P-value ≥ 0.05)

Mortality

Perinatal mortality of all congenital heart diseases is decreasing worldwide. According to *Khoshnood et al.* first-week neonatal mortality of TGA decreased from approximately 19% in the 1983 to 1988 time-period to 3% between 1995 to 2000. First-week mortality was significantly lower for cases of TGA that were diagnosed before birth .The mortality rate was 15.4% for the PND- group compared to 0% in the PND+ group(49)*(Table 3)*.

Bonnet et al. found that prenatal diagnosis reduces mortality and morbidity in TGA concluding that prenatal detection must be increased to improve early neonatal management. They

separated preoperative and postoperative mortality comparing PND+ and PND- groups. In both preoperative and postoperative groups, PND- had a higher mortality rate with an overall rate of 14% versus 0% in the PND+ group(45)*(Table 3)*.

The 2015 study by *Van Velzen et al.* is one of the largest population-based cohort studies of neonates with TGA to date. They found a 0% rate of mortality in TGA patients with a prenatal diagnosis compared to 11.4 % in patients diagnosed postnatally(58)*(Table 3)*.

The *Lara et al.* study collected retrospective data from the Texas birth defects registry from 1999 to 2007 in order to establish whether PND affected patient outcome. Their primary outcome was mortality. They had 10.3% PND+ patients and their findings show that in the overall Texas TGA population, prenatal diagnosis was not significantly associated with improved neonatal survival *(Table 3)*. However, prenatal diagnosis may have the potential to modify outcomes at small volume cardiac surgical centres(47).

Similarly, *Debost-Legrand et al.* found no evidence suggesting that prenatal diagnosis improved survival, whether it was for isolated or associated TGA(46)*(Table 3)*.

Blyth et al. found that there are avoidable deaths when TGA is not recognised before birth. Out of 72 cases of isolated TGA, 5 were detected prenatally and 67 postnatally. The PND+ group had a 0% mortality whereas the PND- group had 11 deaths resulting in a mortality rate of 16.4% *(Table 3).* This was not statistically significant as the numbers of prenatally diagnosed patients were too small(40).

In the *Escobar-Diaz et al.* study there is a 1.2% mortality rate in the PND+ group and a 3.9% rate in the PND- group *(Table 3)*. They explain there was no significant difference in overall mortality once patients who died from complications from BAS were excluded(44).

Table 3 – Influence of prenatal diagnosis on mortality

Study	**Year**	**PND+ (%)[1]**	**PND+ [2]**	**PND- [3]**	**P value**
Lara et al.	2016	10.3	0	10.3	Ns*
Debost-Legrand et al.	2015	24.5	4.4	22.8	Ns
Blyth et al.	2008	6.9	0	16.4	Ns
Escobar-Diaz et al.	2015	23.8	1.2	3.9	Ns
Bonnet et al.	1999	21.4	0	14.0	<0.01
Van Velzen et al.	2015	24.5	0	11.4	<0.009
Khoshnood et al.	2005	72.5	0	15.4	=0.01

[1]PND (%) represents the percentage of TGA patients who were diagnosed prenatally out of all TGA cases in each particular study
[2]Mortality rate in the prenatally diagnosed group (%)
[3]Mortality rate in the postnatally diagnosed group (%)
*Not significant (P-value ≥ 0.05)

Long-term morbidities

The 2004 study by *Bartlett et al.* also studied the impact of prenatal diagnosis on outcomes at one year of age. They had 274 patients available for follow-up at one year of age who underwent an in-person developmental evaluation; of these, 7% had a prenatal diagnosis of TGA. They did not find any differences with statistical differences between the PND+ and PND- groups(48).

In 2012 *Calderon et al.* analysed the effect of PND on neurocognitive outcomes at 4 and 6 years of age. When comparing both groups, significantly better performances in cognitive flexibility and tests of social cognition were observed in the PND+ group. Their results show that prenatal diagnosis of TGA is significantly associated with better score at cognitive flexibility and social cognition tests. It is interesting to note that they also compared TGA patients with controls. Children with TGA had significantly lower scores in most cognitive domains(56). In 2014 *Calderon et al.* performed another study where they compared 38 TGA patients with controls. Their outcomes were facial expression recognition, emotion comprehension and second order cognitive and affective false-belief tasks. They found that children with TGA performed significantly less accurately in the emotion comprehension tasks as well as the second-order affective false belief tasks compared to healthy controls. They do

however mention that prenatal diagnosis was significantly associated with better outcomes once again(59).

Discussion

Prenatal diagnosis of TGA has shown significant benefits in both short and long-term outcomes as well as a decrease in mortality. The rate of TGA prenatal diagnosis is rising worldwide(5). This is explained mainly by the adaptation of screening protocols and a rise in the number of antenatal scans(49,58). Moreover, advances in echo-graphic technology and its increased availability have made the prevalence of prenatal diagnosis rise. In Switzerland, gynaecologists take the responsibility of screening and the possible referral to an adequate centre for delivery if necessary. This procedure has shown an overall prenatal detection rate of 60-70% which is higher than the worldwide average(46).

Advances in obstetrical care as well as progress in surgical techniques are also factors in the decrease of mortality as well as short and long-term morbidities of TGA. It has become clear that prenatal diagnosis allows delivery in a specialized centre which decreases the risk of acute decompensation, profound hypoxia, acidosis and a possible unstable transfer. Prenatal diagnosis generally allows for neonates to obtain quicker initial medical management and maintain more stable hemodynamics(47). This in turn causes a lower rate of ischemic sequelae which is particularly noticeable in long-term neurodevelopmental outcomes(56).

The limitations of this study are twofold. Firstly, perinatal and postoperative mortality were not separated although it seems that prenatal diagnosis mostly affects perinatal mortality. Secondly, the cases of isolated and associated TGA were regrouped as there is very little literature on associated TGA due to its low prevalence. However, it is interesting to note, that when TGA is associated to a co-existing cardiac malformation, its detection rate in utero is higher(53).

Comparing prenatally and postnatally diagnosed TGA patients born in our University hospital (CHUV) would be interesting to evaluate the efficacy of our screening procedure. Evaluation of these patients between 15 to 20 years of age, an important age of individual growth and development, for different neurological outcomes would allow us to observe the effect of prenatal diagnosis on a longer term, which to my knowledge, has not yet been done.

Conclusion

To conclude, prenatal diagnosis of TGA allows for safer delivery in an adequate centre, quicker initial medical management as well as better short and long-term outcomes and lower mortality. A study of TGA patients at 15 to 20 years of age could allow us to have further insight into the impact of prenatal diagnosis on the development of children suffering from TGA.

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